=> file caplus
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FILE COVERS 1907 - 12 Apr 2010 VOL 152 ISS 16
FILE LAST UPDATED: 11 Apr 2010 (20100411/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2010

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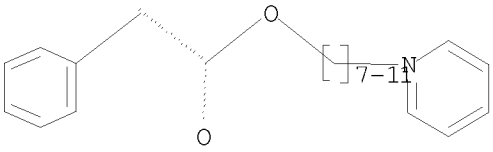
=> d que
L1 STR



Structure attributes must be viewed using STN Express query preparation.
L3 53 SEA FILE=REGISTRY SSS FUL L1
L4 9 SEA FILE=CAPLUS L3

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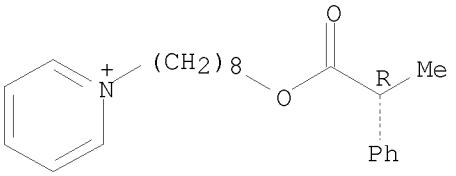
L4 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2009:299030 CAPLUS
DOCUMENT NUMBER: 150:531086
TITLE: Small molecule blockers of the Alzheimer Aβ calcium channel potently protect neurons from Aβ cytotoxicity
AUTHOR(S): Diaz, Juan Carlos; Simakova, Olga; Jacobson, Kenneth A.; Arispe, Nelson; Pollard, Harvey B.
CORPORATE SOURCE: Department of Anatomy, Physiology and Genetics, Uniformed Services University School of Medicine, Bethesda, MD, 20814, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2009), 106(9), 3348-3353
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alzheimer's disease (AD) is a common, chronic neurodegenerative disease that is thought to be caused by the neurotoxic effect of the Amyloid beta peptides (Aβ). We have hypothesized that the intrinsic Aβ calcium channel activity of the oligomeric Aβ polymer may be responsible for the neurotoxic properties of Aβ, and that Aβ channel blockers may be candidate AD therapeutics. As a consequence of a rational search paradigm based on the model structure of the Aβ channel, we have identified two compds. of interest: MRS2481 and an enatiomeric species, MRS2485. These are amphiphilic pyridinium salts that both potently block the Aβ channel and protect neurons from Aβ toxicity. Both block the Aβ channel with similar potency (≈500 nM) and efficacy (100%). However, we find that inhibition by MRS2481 is easily reversible, whereas inhibition by MRS2485 is virtually irreversible. We suggest that both species deserve consideration as candidates for Alzheimer's disease drug discovery.

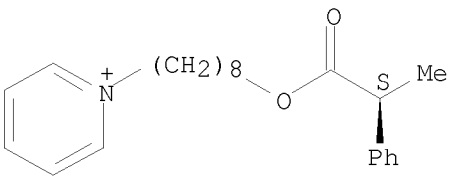
IT 825595-03-7
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MRS2481; small mol. blockers of Alzheimer Aβ calcium channel potently protect neurons from Aβ cytotoxicity)
RN 825595-03-7 CAPLUS
CN Pyridinium, 1-[8-[(2R)-1-oxo-2-phenylpropoxy]octyl]- (CA INDEX NAME)

Absolute stereochemistry.



IT 825595-05-9
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MRS2485; small mol. blockers of Alzheimer Aβ calcium channel potently protect neurons from Aβ cytotoxicity)
RN 825595-05-9 CAPLUS
CN Pyridinium, 1-[8-[(2S)-1-oxo-2-phenylpropoxy]octyl]- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:1354558 CAPLUS
DOCUMENT NUMBER: 146:329570
TITLE: Novel Approaches to Treatment of Autoimmune Neuroinflammation and Lessons for Drug Development
AUTHOR(S): Nizri, Eran; Irony-Tur-Sinai, Michal; Grigoriadis, Nikolaos; Abramsky, Oded; Amitai, Gabi; Brenner, Talma
CORPORATE SOURCE: Laboratory of Neuroimmunology, Department of Neurology, Agnes-Ginges Center for Human Neurogenetics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
SOURCE: Pharmacology (2007), 79(1), 42-49
CODEN: PHMGBN; ISSN: 0031-7012
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Drug development, and especially that intended for central nervous system (CNS) disorders, still poses a challenge. We investigated both the use of bifunctional compds. designed for multiple targeting and enhanced CNS permeability, and of recombinant α-fetoprotein (AFP), a natural pregnancy-associated immunomodulating protein for the treatment of CNS inflammation. Bifunctional compds. showed a novel pharmacokinetic profile due to the conjugation, yet retained, and even improved pharmacodynamics. AFP was well tolerated and decreased various aspects of neuroinflammation, including disease severity, axonal loss and damage, T-cell reactivity, and antigen presentation. Our results show that both strategies may serve as future drug modalities.

IT 452274-24-7 848667-82-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel approaches to treatment of autoimmune neuroinflammation and lessons for drug development)

RN 452274-24-7 CAPLUS
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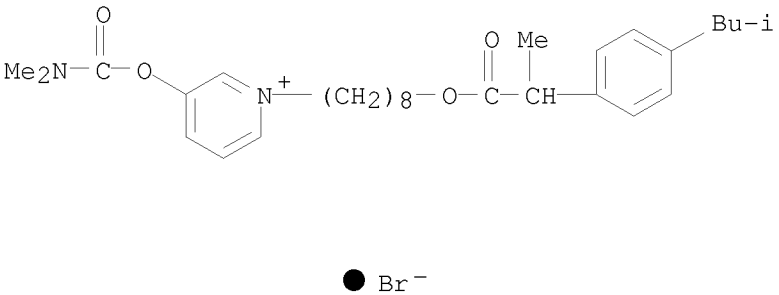

RN 848667-82-3 CAPLUS
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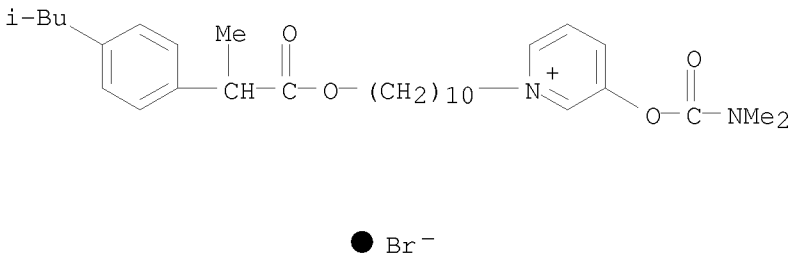

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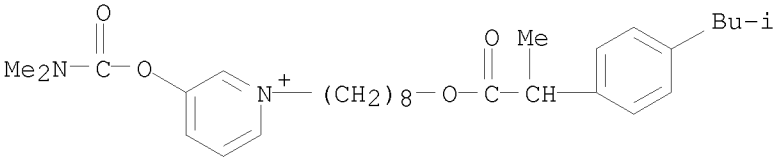
L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2006:129894 CAPLUS
DOCUMENT NUMBER: 145:138823
TITLE: Bifunctional compounds eliciting anti-inflammatory and anti-cholinesterase activity as potential treatment of nerve and blister chemical agents poisoning
AUTHOR(S): Amitai, Gabi; Adani, Rachel; Fishbein, Eliezer; Meshulam, Haim; Laish, Ido; Dachir, Shlomit
CORPORATE SOURCE: Division of Medicinal Chemistry, Israel Institute for Biological Research, Ness Ziona, 74100, Israel
SOURCE: Journal of Applied Toxicology (2006), 26(1), 81-87
CODEN: JJATDK; ISSN: 0260-437X
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Certain organophosphorus (OP) nerve agents (e.g. soman) induce neuroinflammatory processes during acute poisoning. An increased level of typical inflammation markers was also observed in poisoning by alkylating agents such as sulfur mustard (HD). The therapeutic potential of new bifunctional compds. was investigated, eliciting activity of non-steroidal anti-inflammatory drug (NSAID) and anti-cholinesterase (anti-ChE) activity, as an antidotal treatment for both soman and HD poisoning in mice. Three bifunctional compds. were used that include the ChE inhibitor pyridostigmine (PYR) coupled to either ibuprofen (IBU) or diclofenac (DICLO) through an eight (octyl) or ten (decyl) hydrocarbon chain spacer: IBU-PO, IBU-PD and DICLO-PD. These compds. are 15-25 fold less toxic than PYR in mice and exert peripheral and central anti-inflammatory and anti-ChE activity in vivo. IBU-PO (4 mg kg-1, i.p.), IBU-PD (4 mg kg-1, i.p.) and PYR (0.13 mg kg-1, i.p.) reduced to control levels the brain edema in soman-poisoned mice (1.1 LD50, s.c.). Pre-treatment with IBU-PO, IBU-PD and DICLO-PD 4-5 h before soman challenge (2.2-2.3 LD50, s.c.) combined with antidotal treatment (atropine, 11 mg kg-1, 2-PAM-Cl, 25 mg kg-1, i.m.) afforded a longer 24 h survival rate (SR) than with PYR pre-treatment. DICLO-PD exhibited the largest protection efficacy (SR = 70% vs. 17% with PYR). These results indicate a longer duration of action of bifunctional compds. compared with PYR. DICLO-PD (5% in propylene glycol) reduced significantly the HD-induced edema in mouse ear-skin (51% increase in biopsy weight compared with 100% without treatment). Quant. evaluation of ear-skin sections showed that only following DICLO-PD treatment was there a marked decrease in edema. DICLO-PD also elicited a significant decrease in HD-induced vesication as displayed by the reduced sub-epidermal blister level. The data indicate possible use of NSAID-ChEI bifunctional compds. for the medical treatment of both nerve and

alkylating chemical agents.

IT 452274-24-7 848667-82-3 884845-08-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional compds. eliciting anti-inflammatory and anti-cholinesterase activity as potential treatment of nerve and blister chemical agents poisoning)

RN 452274-24-7 CAPLUS
CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)



RN 848667-82-3 CAPLUS
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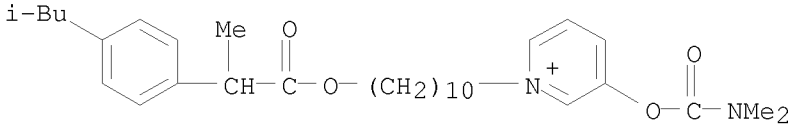
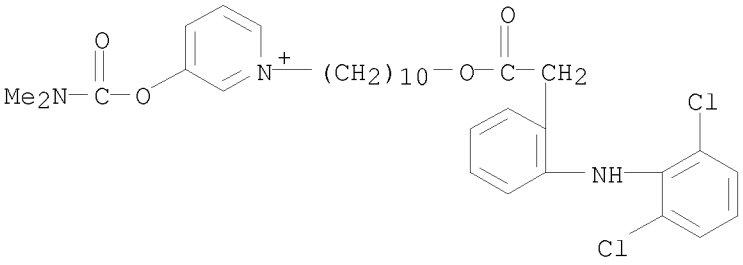
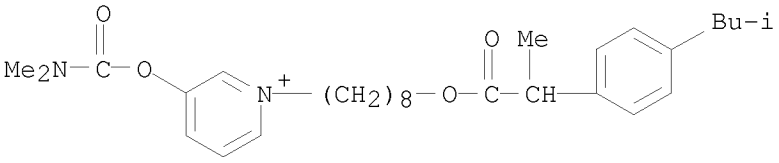


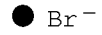
RN 884845-08-3 CAPLUS
CN Pyridinium, 1-[10-[[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]decyl]-3-[[(dimethylamino)carbonyl]oxy]-, bromide (1:1) (CA INDEX NAME)



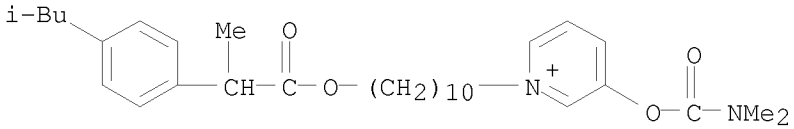
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2005:1302191 CAPLUS
DOCUMENT NUMBER: 144:427015
TITLE: Bifunctional compounds eliciting anti-inflammatory and anti-cholinesterase activity as potential treatment of nerve and blister chemical agents poisoning
AUTHOR(S): Amitai, Gabi; Adani, Rachel; Fishbein, Eliezer; Meshulam, Haim; Laish, Ido; Dachir, Shlomit
CORPORATE SOURCE: Division of Medicinal Chemistry, Israel Institute for Biological Research, Ness Ziona, 74100, Israel
SOURCE: Chemico-Biological Interactions (2005), 157-158, 361-363
CODEN: CBINA8; ISSN: 0009-2797
PUBLISHER: Elsevier Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies cited by Cowan et al. [J. Appl. Toxicol. 23, 177 (2003)] indicate existence of inflammatory and cholinergic pathways in both nerve agents and sulfur mustard (HD) injury. Increase in AChE synthesis and neurite extension was noted after exposure to HD [K.W. Lanks et al., Exp. Cell Res. 355 (1975)]. Moreover, anti-inflammatory drugs reduce the dermal, respiratory and ocular damage caused by exposure to HD. On the other hand, recent studies have noted the involvement of neuro-inflammatory processes during exposure to the nerve agents sarin or soman [Cowan et al., 2003]. The use of various anti-inflammatory drugs in addition to the classical antidotal drugs (e.g. atropine and oximes) caused decrease in certain toxic symptoms and inflammation-induced brain damage. Our new bifunctional drugs (Scheme 1) are based on CNS-permeable mol. combination of pseudo-reversible AChE inhibitor (pyridostigmine, PYR) coupled via a hydrophobic spacer (octyl or decyl hydrocarbon chain) to a non-steroidal anti-inflammatory drug (NSAID) such as Ibuprofen or Diclofenac (Scheme 1). This study evaluates the efficacy of certain bifunctional compds. against HD and soman poisoning in mice in vivo.
IT 452274-24-7 848667-82-3 884845-08-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional compds. eliciting anti-inflammatory and anti-cholinesterase activity as potential treatment of nerve and blister chemical agents poisoning)
RN 452274-24-7 CAPLUS
CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

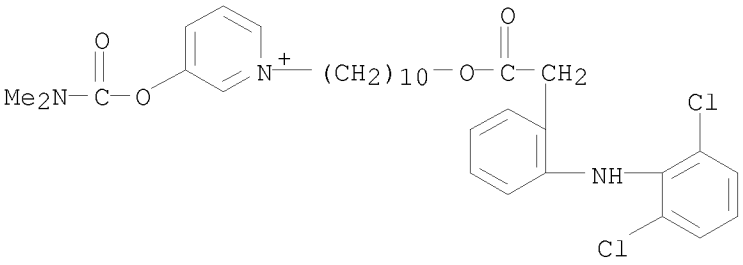




RN 848667-82-3 CAPLUS
CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[10-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]decyl]-, bromide (1:1) (CA INDEX NAME)



RN 884845-08-3 CAPLUS
CN Pyridinium, 1-[10-[[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]decyl]-3-[[(dimethylamino)carbonyl]oxy]-, bromide (1:1) (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2005:581511 CAPLUS
DOCUMENT NUMBER: 143:145818
TITLE: Amphiphilic pyridinium salts block

	TNFα/NFκB signaling and constitutive hypersecretion of interleukin-8 (IL-8) from cystic fibrosis lung epithelial cells
AUTHOR(S):	Tchilibon, Susanna; Zhang, Jian; Yang, QingFeng; Eidelman, Ofer; Kim, Haksung; Caohuy, Hung; Jacobson, Kenneth A.; Pollard, Bette S.; Pollard, Harvey B.
CORPORATE SOURCE:	NIDDK, Laboratory of Bioorganic Chemistry, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE:	Biochemical Pharmacology (2005), 70(3), 381-393 CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER:	Elsevier B.V.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Cystic fibrosis (CF) is a common, lethal genetic disease, which is due to mutations in the CFTR gene. The CF lung expresses a profoundly proinflammatory phenotype, due to constitutive hypersecretion of IL-8 from epithelial cells lining the airways. In a systematic search for candidate drugs that might be used therapeutically to suppress IL-8 secretion from these cells, the authors have identified a potent and efficacious series of amphiphilic pyridinium salts. The most potent of these salts is MRS2481, an (R)-1-phenylpropionic acid ester, with an IC50 of .apprx.1 μM. The authors have synthesized 21 analogs of MRS2481, which have proven sufficient to develop a preliminary structure-activity relationship (SAR). For optimal activity, the authors have found that the ester must be connected to the pyridinium derivative by an eight-carbon chain. An optical isomer of the lead compound, containing an (S)-1-phenylpropionic acid ester, has been found to be a much less active. The mechanism of action of MRS2481 appears to involve inhibition of signaling of the NFκB and AP-1 transcription factors to the IL-8 promoter. MRS2481 is a potent inhibitor of TNFα-induced phosphorylation and proteosomal destruction of IκBα. Inasmuch as IκBα is the principal inhibitor of the NFκB signaling pathway, preservation of intact IκBα would serve to keep the IL-8 promoter silent. The authors also find that MRS2481 blocks TNFα-activated phosphorylation of JNK, the c-JUN kinase. The IL-8 promoter is also activated by an AP-1 site, which requires a phospho-c-JUN/c-FOS dimer for activity. The authors therefore interpret these data to suggest that the mechanism of MRS2481 action is to inhibit both NFκB and AP-1 signaling on the IL-8 promoter. Given the medicinally promising properties of water-solubility, potency in the low μM concentration range, and high efficacy, the authors anticipate that MRS2481, or a further optimized derivative, may find an important place in the armamentarium of pharmaceutical strategies yet to be arrayed against the inflammatory phenotype of the CF lung.

IT 824432-11-3P 824432-12-4P 824432-13-5P
824432-14-6P 824432-15-7P 824432-16-8P
824432-22-6P 824432-23-7P 824432-27-1P
824432-28-2P 824432-29-3P 859723-22-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amphiphilic pyridinium salts block TNFα/NFκB signaling and constitutive hypersecretion of interleukin-8 (IL-8) from cystic fibrosis lung epithelial cells)

RN 824432-11-3 CAPLUS

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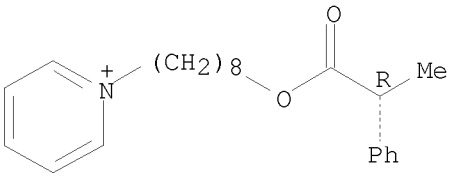
Absolute stereochemistry.



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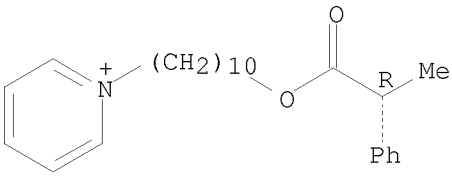
Absolute stereochemistry.



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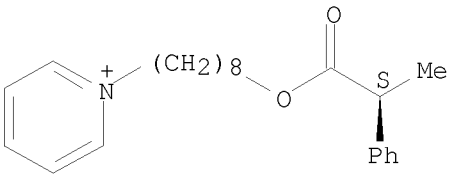
Absolute stereochemistry.



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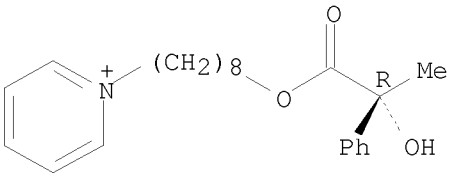
Absolute stereochemistry.



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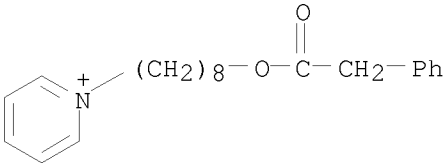

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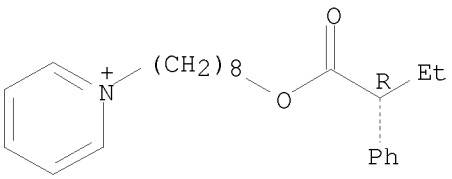
Absolute stereochemistry.



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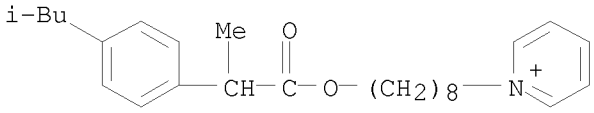

RN 824432-23-7 CAPLUS
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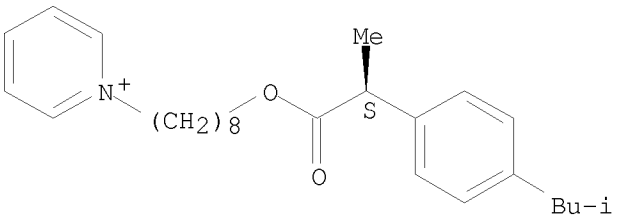
Absolute stereochemistry.



RN 824432-27-1 CAPLUS
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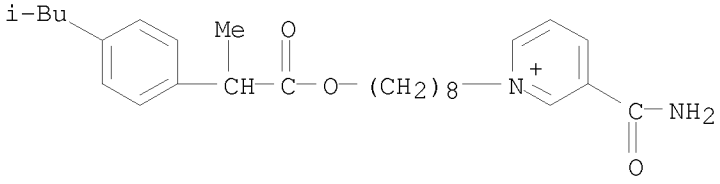
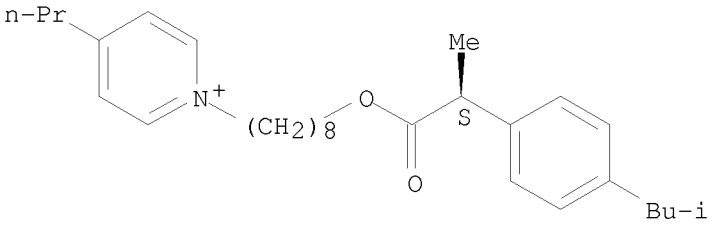


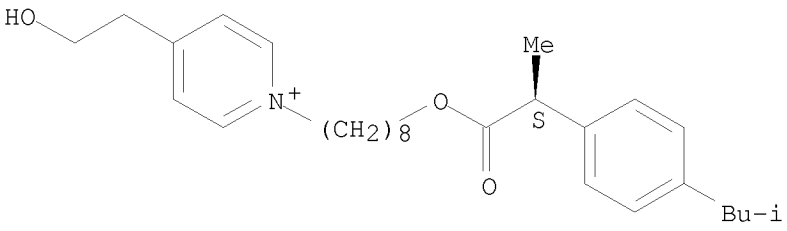
RN 824432-28-2 CAPLUS
CN Pyridinium, 1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-4-propyl-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



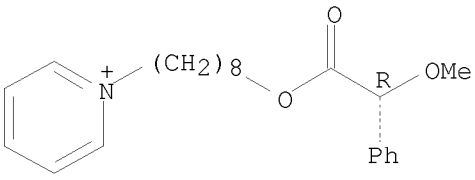
RN 824432-29-3 CAPLUS
CN Pyridinium, 4-(2-hydroxyethyl)-1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



RN 859723-22-1 CAPLUS
CN Pyridinium, 1-[8-[[(2R)-2-methoxy-2-phenylacetyl]oxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.

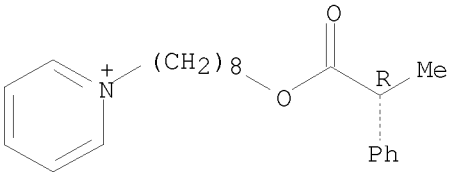


IT 859724-30-4P 859724-32-6P 859724-34-8P
859724-36-0P 859724-38-2P 859724-40-6P
859724-42-8P 859724-52-0P 859724-54-2P
859724-56-4P 859724-58-6P 859724-60-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(amphiphilic pyridinium salts block TNFα/NFκB signaling and constitutive hypersecretion of interleukin-8 (IL-8) from cystic fibrosis lung epithelial cells)

RN 859724-30-4 CAPLUS
CN Pyridinium, 1-[8-[(2R)-1-oxo-2-phenylpropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

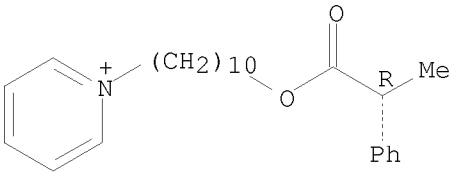
Absolute stereochemistry.



● Br^-

RN 859724-32-6 CAPLUS
CN Pyridinium, 1-[10-[(2R)-1-oxo-2-phenylpropoxy]decyl]-, bromide (1:1) (CA INDEX NAME)

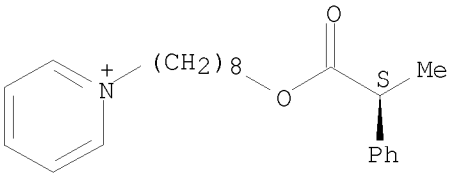
Absolute stereochemistry.



● Br^-

RN 859724-34-8 CAPLUS
CN Pyridinium, 1-[8-[(2S)-1-oxo-2-phenylpropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

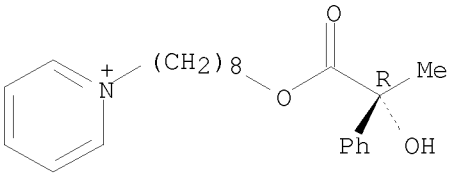
Absolute stereochemistry.



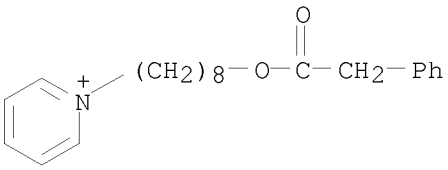
● Br^-

RN 859724-36-0 CAPLUS
CN Pyridinium, 1-[8-[(2R)-2-hydroxy-1-oxo-2-phenylpropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

Absolute stereochemistry.

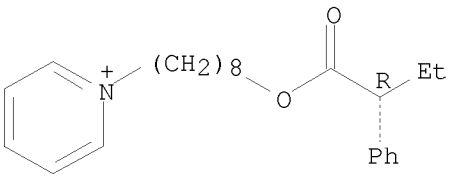


RN 859724-38-2 CAPLUS
CN Pyridinium, 1-[8-[(2-phenylacetyl)oxy]octyl]-, bromide (1:1) (CA INDEX NAME)



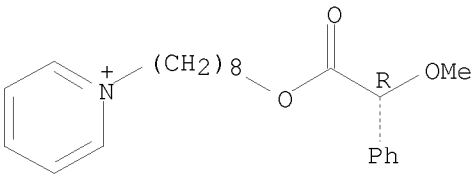
RN 859724-40-6 CAPLUS
CN Pyridinium, 1-[8-[(2R)-1-oxo-2-phenylbutoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



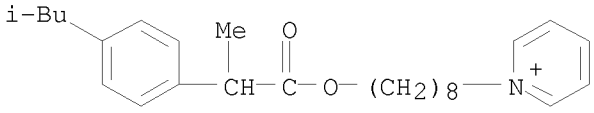
RN 859724-42-8 CAPLUS
CN Pyridinium, 1-[8-[[(2R)-2-methoxy-2-phenylacetyl]oxy]octyl]-, bromide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



● Br^-

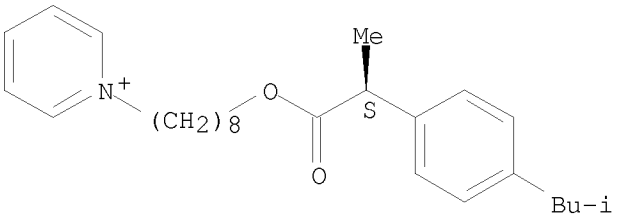
RN 859724-52-0 CAPLUS
CN Pyridinium, 1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)



● Br^-

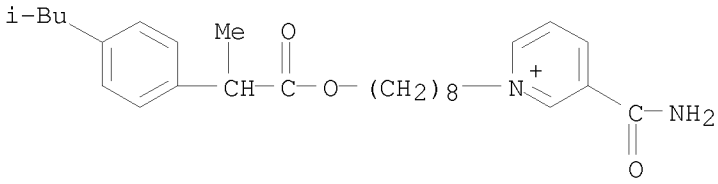
RN 859724-54-2 CAPLUS
CN Pyridinium, 1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



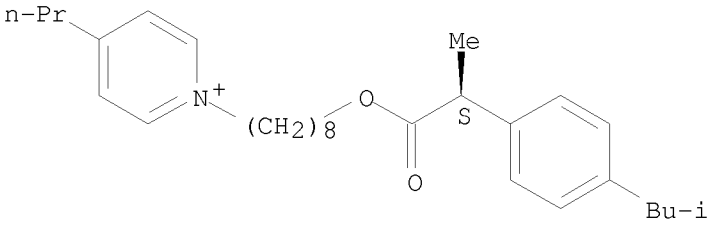
● Br^-

RN 859724-56-4 CAPLUS
CN Pyridinium, 3-(aminocarbonyl)-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)



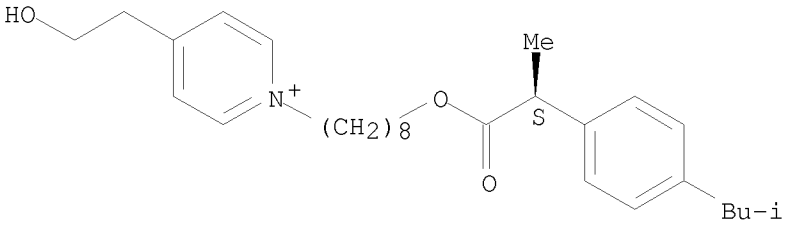
RN 859724-58-6 CAPLUS
CN Pyridinium, 1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-4-propyl-, bromide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



RN 859724-60-0 CAPLUS
CN Pyridinium, 4-(2-hydroxyethyl)-1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

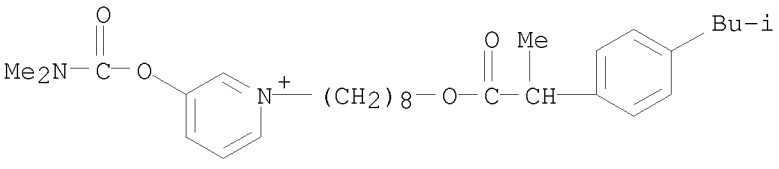
Absolute stereochemistry.



OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

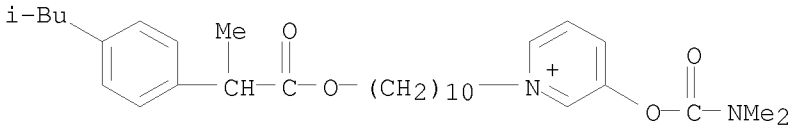
L4 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:93521 CAPLUS
DOCUMENT NUMBER: 142:329315
TITLE: Bifunctional compounds eliciting both anti-inflammatory and cholinergic activity as potential drugs for neuroinflammatory impairments
AUTHOR(S): Nizri, Eran; Adani, Rellie; Meshulam, Haim; Amitai, Gabi; Brenner, Talma
CORPORATE SOURCE: Laboratory of Neuroimmunology, Department of Neurology and the Agnes Ginges Center for Human Neurogenetics, Hadassah-Hebrew University Medical Center, Jerusalem, 91120, Israel
SOURCE: Neuroscience Letters (2005), 376(1), 46-50
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors tested two novel bifunctional compds.: ibuprofen-N-octyl-pyridostigmine bromide (IBU-PO) and ibuprofen-N-decyl-pyridostigmine bromide (IBU-PD). They both contain a nonsteroidal anti-inflammatory drug (NSAID), ibuprofen (IBU) and pyridostigmine (PO), a cholinesterase inhibitor that acts as a cholinergic up-regulator (CURE). The two moieties are conjugated by a hydrocarbon spacer consisting of 8 (octyl) and 10 (decyl) carbons, resp. The compds. were tested for their efficiency in reducing the neurol. symptoms observed in exptl. autoimmune encephalomyelitis induced in mice by myelin oligodendrocyte glycoprotein (MOG). IBU-PO and IBU-PD significantly ameliorated the clin. score (a 40-50% reduction in disease severity) over a period of 30 days, following daily administration of 1 and 0.1 mg/kg, i.p., resp. Clin. improvement was accompanied by reduced responsiveness of MOG-specific T-cells. In addition, IBU-PO and IBU-PD down-regulated the production of nitric oxide (NO) and prostaglandin E2 (PGE2) in cultured astrocytes. To determine which moiety was responsible for these effects, the authors tested each of the two components, IBU and PO. Our findings indicate that combining NSAID with cholinergic intervention contributes an added therapeutic value for each distinct entity and that these bifunctional compds. act both on the peripheral immunol. system and on the central nervous system (CNS) inflammatory pathways.
IT 452274-24-7 848667-82-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional compds. eliciting both anti-inflammatory and cholinergic activity as potential drugs for neuroinflammatory impairments)
RN 452274-24-7 CAPLUS
CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)



RN 848667-82-3 CAPLUS

CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[10-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]decyl]-, bromide (1:1) (CA INDEX NAME)



● Br^-

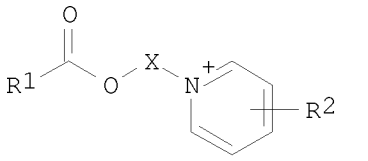
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2005:29162 CAPLUS
DOCUMENT NUMBER: 142:134462
TITLE: A preparation of amphiphilic pyridinium compounds, useful for suppression of IL-8 secretion
INVENTOR(S): Pollard, Harvey; Jacobson, Kenneth
PATENT ASSIGNEE(S): Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002519	A2	20050113	WO 2004-US20718	20040628
WO 2005002519	A3	20050901		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004253541	A1	20050113	AU 2004-253541	20040628
CA 2530075	A1	20050113	CA 2004-2530075	20040628
EP 1638505	A2	20060329	EP 2004-756271	20040628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
US 20070105916	A1	20070510	US 2006-560590	20060627

PRIORITY APPLN. INFO.: US 2003-482764P P 20030627
WO 2004-US20718 W 20040628
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 142:134462; MARPAT 142:134462

GI



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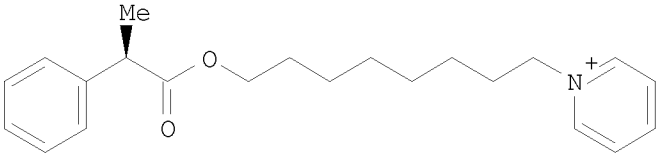


II

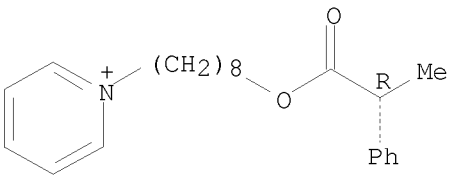
AB The invention relates to a preparation of amphiphilic pyridinium compds., e.g. I•I- [R1 is Ph, benzyl, 2-phenylpropyl, or 1-hydroxy-2-phenylethyl, etc.; R2 is H or 3-C(O)NH2; X is (CH2)n; n = 4, 6, or 8], useful for suppression of IL-8 secretion. The present invention provides methods of making and using such compds. for the treatment of IL-8-related diseases, such as cystic fibrosis. For instance, pyridinium compound II•I- (inhibition of IL-8 secretion: IC50 = 0.35 μM) was prepared from 8-iodooctyl (R)-α-methyl-2-phenylacetate and pyridine with a yield of 45%.

IT 824432-11-3P 824432-12-4P 824432-13-5P
824432-14-6P 824432-15-7P 824432-16-8P
824432-17-9P 824432-22-6P 824432-23-7P
824432-24-8P 824432-26-0P 824432-27-1P
824432-28-2P 824432-29-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amphiphilic pyridinium compound useful for suppression of IL-8
secretion)

RN 824432-11-3 CAPLUS

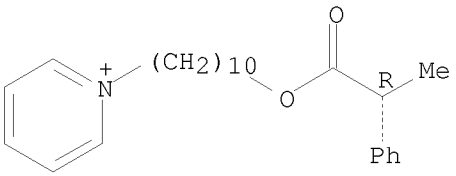
CN Pyridinium, 1-[8-[(2R)-1-oxo-2-phenylpropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



RN 824432-12-4 CAPLUS
CN Pyridinium, 1-[10-[(2R)-1-oxo-2-phenylpropoxy]decyl]-, iodide (1:1) (CA INDEX NAME)

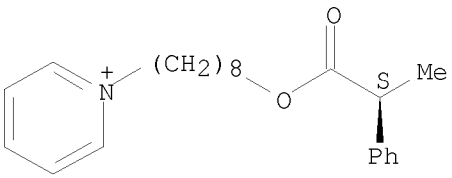
Absolute stereochemistry.



● I^-

RN 824432-13-5 CAPLUS
CN Pyridinium, 1-[8-[(2S)-1-oxo-2-phenylpropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

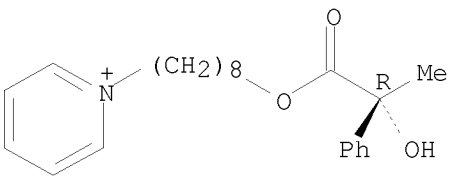
Absolute stereochemistry.



● I^-

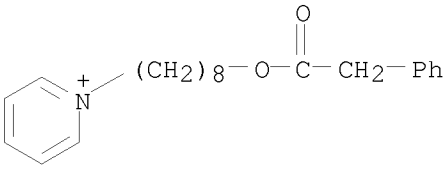
RN 824432-14-6 CAPLUS
CN Pyridinium, 1-[8-[(2R)-2-hydroxy-1-oxo-2-phenylpropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



● I^-

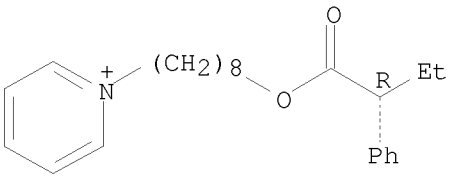
RN 824432-15-7 CAPLUS
CN Pyridinium, 1-[8-[(2-phenylacetyl)oxy]octyl]-, iodide (1:1) (CA INDEX NAME)



● I^-

RN 824432-16-8 CAPLUS
CN Pyridinium, 1-[8-[(2R)-1-oxo-2-phenylbutoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

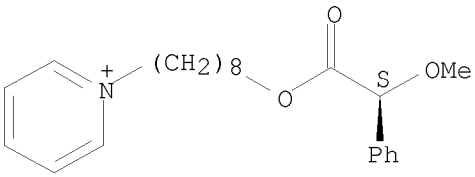
Absolute stereochemistry.



● I^-

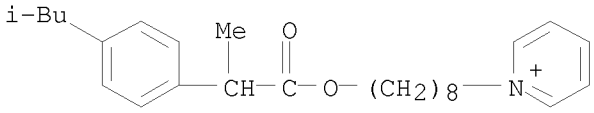
RN 824432-17-9 CAPLUS
CN Pyridinium, 1-[8-[[(2S)-2-methoxy-2-phenylacetyl]oxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



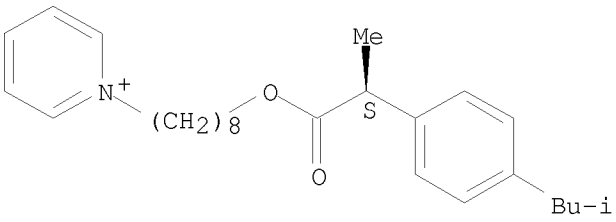
● I^-

RN 824432-22-6 CAPLUS
CN Pyridinium, 1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

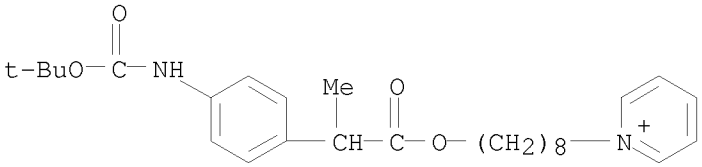


RN 824432-23-7 CAPLUS
CN Pyridinium, 1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



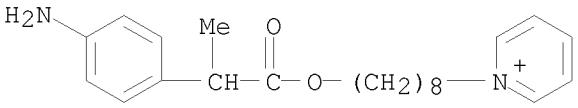
RN 824432-24-8 CAPLUS
CN Pyridinium, 1-[8-[2-[4-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)



RN 824432-26-0 CAPLUS
CN Pyridinium, 1-[8-[2-(4-aminophenyl)-1-oxopropoxy]octyl]-, iodide, 2,2,2-trifluoroacetate (1:1:1) (CA INDEX NAME)

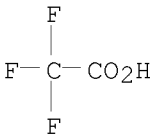
CM 1

CRN 847165-10-0
CMF C22 H31 N2 O2 . I

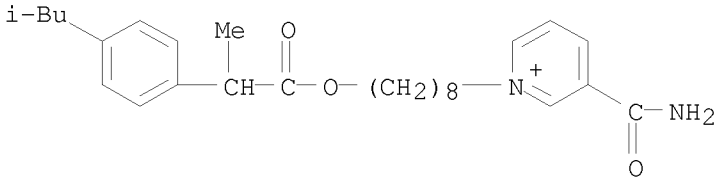


CM 2

CRN 76-05-1
CMF C2 H F3 O2

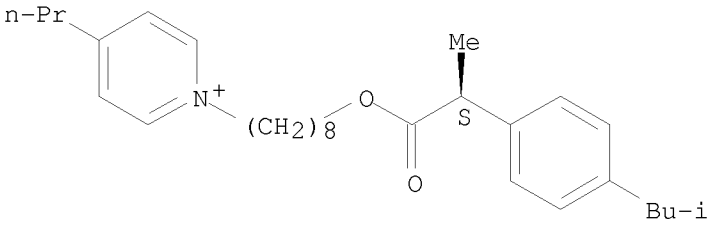


RN 824432-27-1 CAPLUS
CN Pyridinium, 3-(aminocarbonyl)-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)



RN 824432-28-2 CAPLUS
CN Pyridinium, 1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-4-propyl-, iodide (1:1) (CA INDEX NAME)

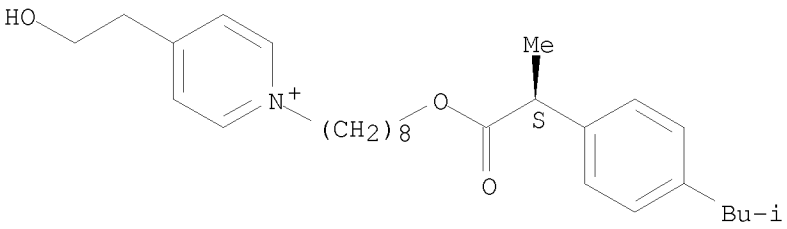
Absolute stereochemistry.



● I⁻

RN 824432-29-3 CAPLUS
CN Pyridinium, 4-(2-hydroxyethyl)-1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)

Absolute stereochemistry.



● I⁻

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

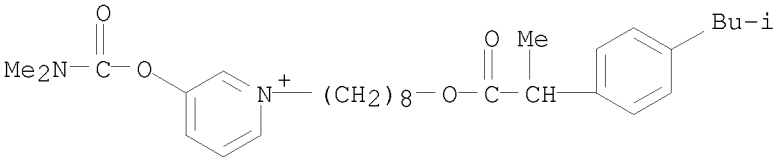
L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2004:936826 CAPLUS
DOCUMENT NUMBER: 142:384739
TITLE: Bifunctional compounds eliciting both anti-inflammatory and cholinergic activity as potential drugs for CNS disorders
AUTHOR(S): Amitai, G.; Adani, R.; Rabinovitz, I.; Beit-Yanai, E.; Shohami, E.; Sod-Moriah, G.; Meshulam, H.
CORPORATE SOURCE: Division of Medicinal Chemistry, IIBR, Ness-Ziona, Israel
SOURCE: Cholinergic Mechanisms: Function and Dysfunction, [International Symposium on Cholinergic Mechanisms], 11th, St. Moritz, Switzerland, May 5-9, 2002 (2004), Meeting Date 2002, 277-288. Editor(s): Silman, Israel. Taylor & Francis Ltd.: London, UK. CODEN: 69GBA2; ISBN: 1-84184-075-0
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. The involvement of hypocholinergic activity and inflammatory markers in certain central nervous system (CNS) disorders suggests that combination of cholinergic enhancement together with anti-inflammatory potency may be beneficial for the treatment of these CNS disorders. The

pharmacol. activity of novel bifunctional compds. comprising certain NSAIDS and pyridostigmine (PYR), and particularly ibuprofen-octyl-pyridostigmine bromide (IBU-PO) is described. In particular, the synthesis of these compds., their structure, inhibition kinetics, hypothermic effect, lipophilicity, acute toxicity and therapeutic index, peripheral anti-inflammatory activity, anti-inflammatory activity in brain, protection against closed head injury, and protection against hypobaric hypoxia are discussed.

IT 452274-24-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional compds. eliciting both anti-inflammatory and cholinergic activity as potential drugs for CNS disorders)

RN 452274-24-7 CAPLUS

CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)



● Br^-

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:657907 CAPLUS
DOCUMENT NUMBER: 137:195592
TITLE: Chimeric compounds co-inducing cholinergic up-regulation and inflammation down-regulation, and use for treatment and/or prevention of central nervous system diseases
INVENTOR(S): Amitai, Gabriel; Adani, Rachel; Rabinovitz, Ishai; Sod-Moriah, Gali; Meshulam, Haim
PATENT ASSIGNEE(S): Israel Institute for Biological Research, Israel; Life Science Research Israel Ltd.
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002065977	A2	20020829	WO 2002-IL122	20020217
WO 2002065977	A3	20031204		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
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US 20020160988	A1	20021031	US 2001-906952	20010716
CA 2439898	A1	20020829	CA 2002-2439898	20020217
AU 2002232100	A1	20020904	AU 2002-232100	20020217
EP 1385824	A2	20040204	EP 2002-712224	20020217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004537504	T	20041216	JP 2002-565538	20020217

PRIORITY APPLN. INFO.:
US 2001-269343P P 20010220
US 2001-906952 A 20010716
WO 2002-IL122 W 20020217

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

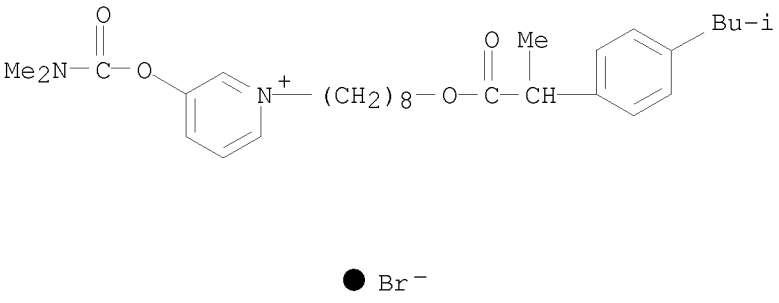
OTHER SOURCE(S): MARPAT 137:195592

AB Chimeric compds. are disclosed which are covalent conjugates of reversible or irreversible cholinergic up-regulators and nonsteroidal antiinflammatory drugs (NSAIDs). Also disclosed are methods for their synthesis and use thereof for treatment and/or prevention of central nervous system (CNS) disorders and diseases.

IT 452274-24-7P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(chimeric compds. co-inducing cholinergic up-regulation and inflammation down-regulation, and use for treatment and/or prevention of central nervous system diseases)

RN 452274-24-7 CAPLUS

CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

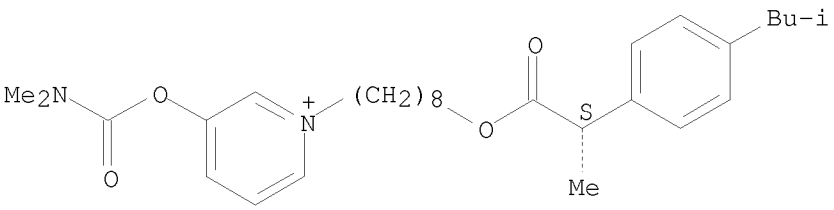


IT 452274-25-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(chimeric compds. co-inducing cholinergic up-regulation and inflammation down-regulation, and use for treatment and/or prevention of central nervous system diseases)

RN 452274-25-8 CAPLUS

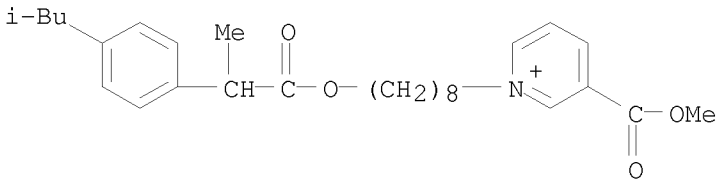
CN Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-[8-[(2S)-2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, bromide (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



● Br^-

IT 452274-40-7P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(reaction; chimeric compds. co-inducing cholinergic up-regulation and inflammation down-regulation, and use for treatment and/or prevention of central nervous system diseases)
RN 452274-40-7 CAPLUS
CN Pyridinium, 3-(methoxycarbonyl)-1-[8-[2-[4-(2-methylpropyl)phenyl]-1-oxopropoxy]octyl]-, iodide (1:1) (CA INDEX NAME)



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OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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